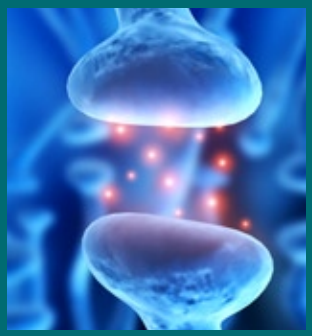
CDMRP
Department of Defense

Tuberous Sclerosis Complex Research Program

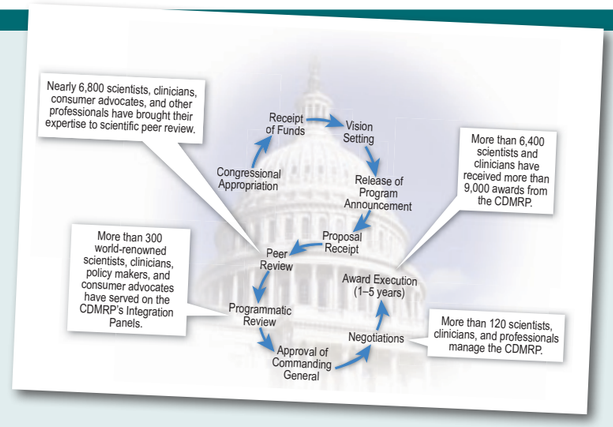

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

HISTORY In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that implored Congress to appropriate funds for breast cancer research. This created a unique partnership among the public, Congress, and the military. Since that time, the CDMRP has grown to encompass multiple targeted programs and has received over $5.3 billion in appropriations from its inception in fiscal year 1993 (FY93) through FY09. Funds for the CDMRP are added to the Department of Defense (DOD) budget, where support for individual programs such as the Tuberous Sclerosis Complex Research Program (TSCRP) is allocated via specific guidance from Congress.

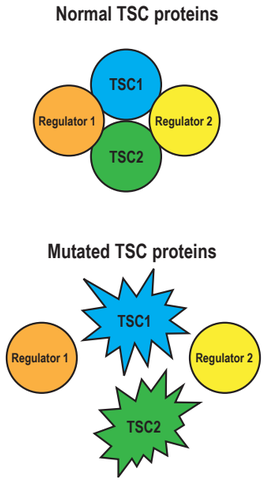
Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interaction among scientists, clinicians, representatives from the military services, and consumer advocates. The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. The second tier is a programmatic review of proposals that compares submissions to each other and recommends proposals for funding based on scientific merit, portfolio balance, and relevance to individual program goals.

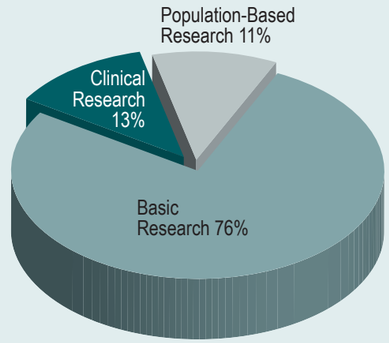


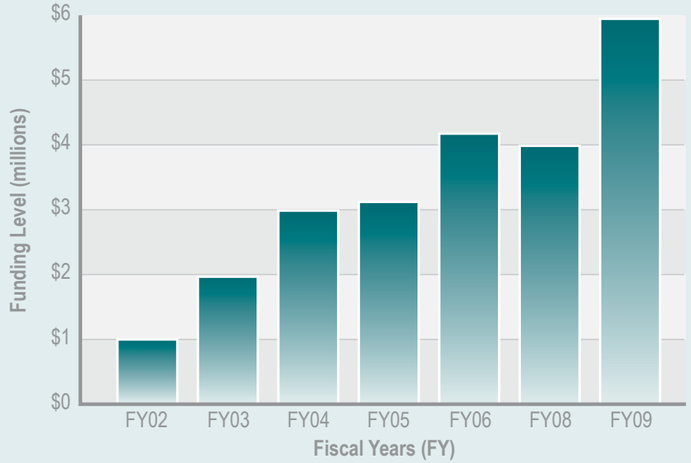
The Disease:

Tuberous sclerosis complex (TSC) is a genetic disorder that affects as many as 50,000 individuals in the United States and about 1 to 2 million individuals worldwide. TSC causes tumors in many different organs, especially in the brain, eyes, heart, kidney, skin, and lungs. TSC is also characterized by seizures, developmental delays, behavioral problems, autism, and mental retardation. Major research breakthroughs have identified two genes, TSC1 and TSC2, whose dysfunction causes TSC. The TSC1 gene is located on chromosome 9 and produces a protein called TSC1 (hamartin). The TSC2 gene is located on chromosome 16 and produces a protein called TSC2 (tuberin). These proteins normally interact with each other and with important cell regulatory proteins; mutations in TSC1 or TSC2 disrupt these communications. The discovery of the TSC1 and TSC2 genes is a giant step forward in the fight against TSC, as they provide excellent targets for the development of new diagnostic assays and therapies for TSC.



TSC FY02–06 and FY08 Portfolio by Research Area





Tuberous Sclerosis Complex Research Program

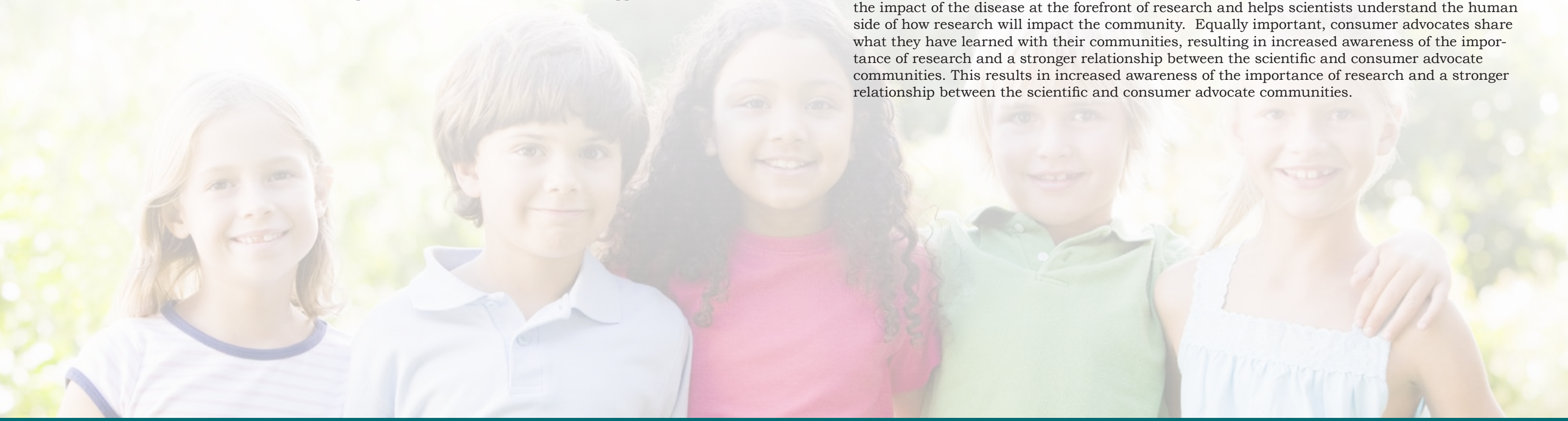
VISION

To lessen the impact of TSC.

MISSION

To encourage innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC.

Grassroots efforts by the TSC advocacy community led to congressional appropriations to the DOD of $1 million (M) in FY02 for TSC research. Since then, a total of $23.5M has been appropriated, including $6M for FY09. This funding energized the development of a unique partnership among the public, Congress, and the military. The CDMRP within the U.S. Army Medical Research and Materiel Command (USAMRMC) manages the TSCRP. The TSCRP is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from the scientific community, advocacy groups, and Congress. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States. The TSCRP fills important gaps in TSC research not addressed by other funding agencies. The TSCRP vision is adapted yearly to facilitate rapid change and to better target funding to the most critical TSC research areas, thus ensuring that the program remains responsive to current needs and future opportunities.



Building Partnerships

The successes of the TSCRP have and continue to be critically dependent on strong partnerships. Consumer advocates, peer review panel members, Integration Panel (IP) members, and the scientific community have worked synergistically to achieve the goal of lessening the impact of TSC. The combination of their diverse expertise has generated ideas that have hastened TSC research.

Consumer Advocates

Consumer advocates for the TSCRP may be individuals with TSC or those who have family members with TSC (TSC initially manifests in childhood). As active members of the TSCRP, consumer advocates participate in the peer review of proposals as well as in setting program priorities and making funding recommendations. Approximately 15 consumer advocates have contributed to both peer and programmatic review since 2002. Consumer advocates' firsthand experiences with TSC provide a unique perspective that is complementary to the expertise of the scientists and clinicians. This perspective keeps the urgency of lessening the impact of the disease at the forefront of research and helps scientists understand the human side of how research will impact the community. Equally important, consumer advocates share what they have learned with their communities, resulting in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities. This results in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities.

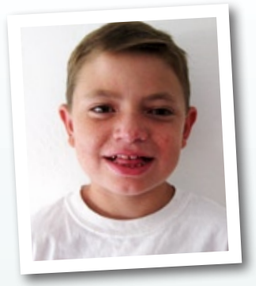
From Lemons to Lemonade, SeizureTracker.com

Rob Moss, Tuberous Sclerosis Complex Research Program Integration Panel member and Co-founder of SeizureTracker.com

Rob and Lisa Moss believe and live by the motto "when life hands you lemons, make lemonade." Their son was diagnosed at an early age with tuberous sclerosis complex (TSC), an inherited disease that causes benign tumors in the brain, eyes, kidneys, skin, lungs, or heart. TSC is associated with epilepsy and developmental delays. While Rob and Lisa's son has no significant developmental delays, he does have seizures caused by the benign brain tumors. They noticed their son's first seizure when he was 4 weeks old. Early on, these seizures were subtle, relatively infrequent (only about once every 3 months), partial seizures (affecting his left side) that lasted for 30 seconds. By the time their son was 3½, these partial seizures increased in number and duration. The seizures lasted up to 2 minutes, and in 1 month the number of seizures peaked at 350. After their initial visit to a neurologist, Rob and Lisa were given a paper chart with 365 blocks to track their son's seizures. When the seizures were relatively infrequent, this was an adequate way to track them, but when they peaked at 350 in 1 month, it became overwhelming. Rob and Lisa began looking for online tools to help them track their son's seizures but were unable to find any. So with these "lemons," Rob and Lisa developed the "lemonade" known as SeizureTracker.com, a free online tool for tracking seizures, medications, doctor's appointments, and daily notes. People started using SeizureTracker.com the very first night it was launched in November 2007, and now there are nearly 2,000 users worldwide. From life's lemons, Rob and Lisa Moss made lemonade enjoyed by a global community. Of the website Rob said, *"Our family is forever indebted to both the epilepsy and TSC communities for all the support they have and still give us; the website is the least we can do to give back."* Their son eventually had surgery to remove the benign brain tumors and now is virtually seizure free.

Rob is a member of the CDMRP's Tuberous Sclerosis Complex Research Program (TSCRP) Integration Panel (IP). Of his experience on the TSCRP IP, Rob said, *"With an extraordinary commitment to tuberous sclerosis, the TSCRP acts as a mechanism to bring multidisciplinary professionals and individuals together to work as a team defining the direction of TSC-related research. I have had the honor and privilege to see firsthand how intensely dedicated this group is to improving the lives of those affected by tuberous sclerosis. Because my son struggles with many issues associated with TSC, research funded through the TSCRP has had a direct effect on my family and we look to this program as a beacon of hope."*

Consumer Peer Reviewers



Debora Moritz was an FY09 Consumer Peer Reviewer. Her son Griffin has tuberous sclerosis. He is almost 12 years old now. He was diagnosed when he was 5 months old after he began having infantile spasms. His seizures were exceptionally hard to get under control. He has never been seizure free. Yet, Griffin is a happy, funny active child. For a period of time he had to wear a helmet to protect him when he had drop seizures. Over the years he has taken 11 different anti-epileptic medications individually or in various combinations. They have all pretty much failed to completely control his seizures that have changed over the years.

This past October the subependymal nodules that we had been monitoring for some years showed an explosion of growth making them full-fledged subepedymal giant cell astrocytomas that were beginning to cause hydrocephalous. In the past surgery was the only option. Fortunately, Griffin was able to qualify for a clinical trial of RAD001 for the treatment of astrocytomas. In 3 months it shrank them enough for the ventricles to return to normal size and shape. We continue on with this medication to try and shrink the astrocytomas to the point of atrophy. Just a few years ago this option would not have been available.

Of her experience as a consumer peer reviewer Debora says, *"Living with tuberous sclerosis complex, because of its huge variation in expression and unpredictable course of progression, can be a very frustrating experience. Lobbying for increased research funding has been one outlet for that frustration where I felt I could make a positive impact for individuals with TSC. Serving as a consumer advocate for the CDMRP peer review process, acting as the voice for tens of thousands of individuals with TSC and their families was a fearsome responsibility. The process demonstrated to me that the CDMRP for tuberous sclerosis is a program that will generate meaningful interventions for tuberous sclerosis not just far into the future but in my son's lifetime. The CDMRP attracts talented, innovative researchers passionate about their science and responsive to consumer's desire for urgency in application. I was humbled to be a part of the process and now more than ever I can confidently lobby for increased funding for such an impactful mechanism of meaningful research."*

Ron Heffron's 5 year-old son has TSC2. He was diagnosed at age 5 months due to his infantile spasms, which were not controlled with medications. He underwent a three-stage resection at age 13 months, followed by a single-stage resection at 22 months old. He still has some seizures, though much more mild than what he experienced prior to surgery. Ron, an FY08 and FY09 consumer peer reviewer said, *"Serving on the peer review panel for TSC has been the single most rewarding experience of my journey with TSC to date. With my wife focused on the daily care issues, this is the single most important thing I can do for my son and his future."*

Peer Review Panel Members

Scientific peer review is conducted by panels of expert scientists, clinicians, and consumer advocates who provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the TSCRP. Peer review panels are typically organized by scientific discipline and specialty areas. To date, over 90 scientists, clinicians, and consumer advocates have brought their expertise to the TSCRP scientific peer review process.

Dr. Douglas C. Miller, FY04 and FY05 Scientific Peer Reviewer, trained in neuropathology from 1982–84 at the Massachusetts General Hospital in Boston and has been an active academic diagnostic neuropathologist ever since. Other than diagnostic work, his involvement with TSC work dates back 15 years. *"As a peer reviewer I have greatly enjoyed reviewing innovative cutting-edge research proposals, and I have learned much from my reviews and from following the progress of TSC research as these proposals have evolved over the years."*

Dr. Steven Sparagana, FY08 and FY09 Scientific Peer Reviewer, got involved in clinical aspects of TSC research about 14 years ago, shortly after joining the TSC Clinic at Texas Scottish Rite Hospital for Children in Dallas, Texas as a staff pediatric neurologist. He conducts clinical research involving children with TSC, like the now international TSC Natural History Database. He said, *"The community of individuals with TSC has benefitted greatly from the basic science and clinical initiatives funded by the CDMRP TSC research program. I am honored to have participated in a grant funded by this program, and I am equally happy to have recently served as a peer reviewer for the program."*

During her pediatric neurology training at the Mayo Clinic, FY09 Scientific Peer Reviewer, **Dr. Martina Bebin,** had Dr. Manuel Gomez as a mentor. Spending time seeing TSC patients with him, she developed a keen interest in the condition and worked on several clinical research projects. Now nearly 20 years later, she works on new treatment options for patients with TSC and clinical research projects that broaden our understanding of the TSC phenotype-genotype. Of her experience as a peer reviewer, Dr. Bebin said, *"It was a valuable experience to participate in the peer review process. I was very impressed with the investigators scientific originality in the grant proposals and their ability to build on current scientific knowledge to advance the field of TSC research."*

Integration Panel Members

The TSCRP IP is composed of 8 prominent scientists, clinicians, and consumer advocates with varied expertise in TSC. IP members use their knowledge and expertise to develop and recommend an annual vision and investment strategy for the TSCRP that focuses on innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC. Additionally, IP members review proposals and suggest a broad-based research portfolio that best meets the program's vision and mission.

FY09 IP Members

E. Steve Roach, M.D. (Chair)
The Ohio State University

Steven Chin, M.D., Ph.D.
University of Utah Health Sciences Center

David Dunn, M.D.
Indiana University School of Medicine

Jane Fountain, Ph.D.
National Institute of Neurological Disorders and Stroke

David Kwiatkowski, M.D., Ph.D.
Brigham and Women's Hospital

Hiroaki Onda, Ph.D.
Tuberous Sclerosis Alliance

Sabita Sankar, Ph.D.
Signal Pharmaceuticals, LLC Division of Celgene Corporation

Tian Xu, Ph.D.
Yale University School of Medicine

Dr. Steve Roach was the FY09 Integration Panel Chair. His interest in TSC dates to one particular child during his pediatric internship—a normally intelligent girl who died from a giant cell tumor. At the time, both normal intelligence and giant cell tumors were considered very rare in individuals with TSC. This interest evolved into a more general interest in phenotypic variability in TSC, the categorization of TSC features into levels of specificity for use in diagnostic criteria and genetics. Of his service on the IP, Dr. Roach said, *"It has been a fascinating and stimulating endeavor. It forces one to delve into areas of research that are unfamiliar and to see familiar areas in new light."*

Dr. David Kwiatkowski, FY09 Integration Panel Member, is a medical oncologist who became interested in TSC research about 20 years ago. He has focused on many aspects of TSC including: identification of the TSC1 gene; the human molecular genetics of TSC; mosaicism in TSC; development and analysis of mouse models of TSC; definition of the functions and signaling patterns of the TSC proteins TSC1 and TSC2; and treatment approaches in TSC. Of his IP experience, he said, *"I thought that it was an important forum in which consideration was given to the overall research support there is for TSC research, the balance of the overall portfolio (including NIH and foundations), as well the evaluation of each individual proposal."*

Scientific Community

The TSCRP has funded 56 scientists and clinicians across the nation and abroad. TSCRP-supported investigators are engaged in cutting-edge work to find a cure for TSC. Through creative approaches and ideas, investigators are gaining momentum toward the goal of lessening the impact of TSC, as reflected in the success stories described in the remainder of this chapter.

The TSCRP has implemented research award mechanisms that are specifically aimed at minimizing the impact of TSC. To fill important research gaps, the TSCRP has focused on three broad areas:

- **Exploring Innovative, Groundbreaking Ideas and Technology:** Supporting high-risk and high reward research of exciting new ideas. Concept Awards fund high-risk, high-reward research toward the exploration of novel theories and development of new preclinical tools. Idea Development Awards encourage innovative research directed toward the pathogenesis of TSC and improving its diagnosis and treatment.
- **Retaining Young Scientists in TSC Research:** The Career Transition Awards support TSC researchers during the transition from postdoctoral training to an independent position. This award has the unique feature of funding up to 2 years of postdoctoral training followed by up to 2 years of a faculty-level position. The Career Transition Awards address the important issue of retaining young scientists in TSC research and helps maintain the momentum and expansion of discoveries from a postdoctoral project into a new, independent TSC research laboratory.
- **Impacting Patients' Lives:** The Natural History Awards fund focused, hypothesis-driven natural history studies to enhance the current knowledge of TSC manifestations and improve clinical management.

Exploring Innovative, Groundbreaking Ideas and Technology

Concept Awards and Idea Development Awards

Zebrafish Model Reveals Functional Connection Between the Cilium and TSC Genes

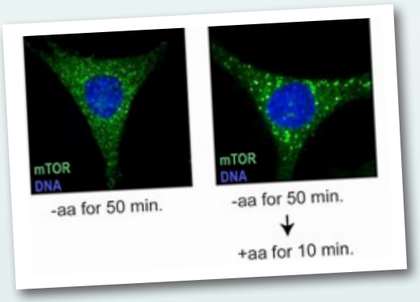
Zhaoxia Sun, Ph.D.
Yale University School of Medicine
FY06 Concept Award Recipient

Cilia are cell surface organelles that protrude into the microenvironment and function like antennae for the cell. Recent advances suggest that in vertebrate cells, the cilia function as sensory organelles for multiple signaling pathways. Studies in multiple model systems have shown that defects in cilia formation and function on renal epithelial cells lead to kidney cysts, which are epithelium-lined and liquid-filled sacs. Defects in cilia formation or function can also lead to early developmental deficiencies, most notably abnormal left–right asymmetry of the body plan. Kidney cyst formation is one of the complications of TSC, which is caused by inactivating mutations of the TSC1 and TSC2 tumor suppressor genes. The TSC1 and TSC2 genes' protein products form a complex in the target of rapamycin (TOR) pathway that incorporates environmental signals to regulate cell growth, proliferation, and survival. The critical role of the cilium in kidney cyst formation, together with the observation of kidney cyst formation in TSC patients and rodent models, prompted Dr. Zhaoxia Sun to ask whether there is a functional connection between the cilium and TSC genes. She hypothesized that the cilium may regulate the TSC/TOR pathway. Her lab tested the hypothesis by examining TSC1 loss-of-function phenotypes and the status of the TOR pathway in available ciliary mutants in the zebrafish model system. Two TSC1 homologs, referred to as tsc1a and tsc1b, were identified in zebrafish. Her group observed that knockdown of tsc1a in zebrafish leads to body curvature, kidney cyst formation, and defects in establishing left–right asymmetry of the body plan, phenotypes characteristic of ciliary mutants. Furthermore, the researchers found that kidney cyst formation in ciliary mutants was blocked by the TOR inhibitor, rapamycin. Their study provided phenotypic, genetic, and biochemical evidence to support the existence of a functional link between the cilium and the TSC/TOR pathway.

TSC1 and TSC2 Variants Identified in Patients with Tuberous Sclerosis Complex

Mark Nellist, Ph.D.
Erasmus MC-Daniel den Hoed Cancer Center Rotterdam, The Netherlands
FY06 Idea Development Award Recipient

Mutation analysis of the TSC1 and TSC2 genes is a valuable diagnostic tool for TSC, and in most cases a definite disease causing TSC1 or TSC2 mutation is identified. However, there are some unclassified variants in which it is difficult to determine whether sequence changes identified in the TSC1 or TSC2 genes are pathogenic. These variants present significant diagnostic and genetic counseling challenges. Dr. Mark Nellist is developing and applying assays to determine whether specific unclassified TSC1 and TSC2 variants are pathogenic. Results of these studies will provide clearer information about TSC and the associated risks to individuals and families carrying these variant mutations. Additionally, these studies could provide insight into genotype-phenotype correlations and identify regions of these proteins that are important for TSC1 and TSC2 function. Using an immunoblot assay, Dr. Nellist has identified three regions essential for TSC1 or TSC2 function: (1) amino acid substitutions within the N-terminal region (amino acids 1–200) of TSC1 that destabilize TSC1, (2) substitutions to a central region of TSC2 (amino acids 600–900) that disrupt TSC1–TSC2 binding, and (3) substitutions outside the predicted TSC2 GAP domain that inactivate the complex. He has also identified a region of TSC1 (amino acids 50–224) required for maintaining TSC1 at sufficient levels in the cell to form a stable TSC1–TSC2 complex and inhibit mTOR.



The Rags Necessary to Mediate Amino Acid Signaling to mTORC1

David Sabatini, M.D., Ph.D.
Whitehead Institute for Biomedical Research
FY06 Idea Development Award Recipient

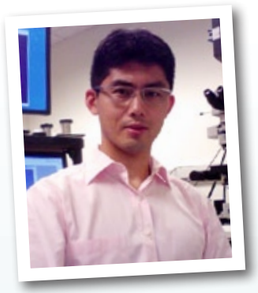
The protein kinase mammalian target of rapamycin (mTOR) plays a central role in cell growth, proliferation, and survival. The deregulation of the mTOR pathway has been implicated in many human diseases. In TSC, the mTOR pathway is hyperactive. mTOR participates in two distinct multi-protein complexes, one of which is the mTOR complex 1 (mTORC1). The mTORC1 protein complex has recently emerged as a key downstream regulator of TSC1/2. Although mTORC1 is a major therapeutic target, little is known about its structure and the molecular mechanisms through which TSC1/2 regulates the mTOR kinase.

Raptor (regulatory-associated protein of mTOR) is one of the mTOR-interacting proteins being studied by Dr. David Sabatini. While analyzing the Rheb-mediated phosphorylation of Raptor in the regulation of mTORC1, Dr. Sabatini found a new Raptor-interacting protein, RagC. The Rag proteins are a unique family of small GTPases that have been shown to interact with each other in mammalian cells and in yeast. In mammals, there are four Rag genes, Rag A, B, C, and D. Dr. Sabatini found that binding of the Rag GTPase to Raptor is necessary to trigger amino acid signaling to mTORC1 and that binding also causes the amino acid–induced relocalization of mTOR within the endomembrane system of the cell. Given the prevalence of cancer-linked mutations in the pathways that control mTORC1, Dr. Sabatini suggests that Rag function is also deregulated in human tumors. Dr. Sabatini is currently assessing the details of amino acid-induced mTORC1 activation while trying to identify other Rag-interacting proteins.

Angiogenesis and Lymphangiogenesis as Chemotherapeutic Targets in Tuberous Sclerosis Complex

Thomas Darling, M.D., Ph.D.
Uniformed Services University of the Health Sciences
FY08 Idea Development Award Recipient

Patients with TSC develop skin tumors that bleed with minor trauma and can be disfiguring. There are no effective oral or topical treatments for these TSC skin tumors. As a result, patients must undergo several surgical procedures that can ultimately leave scarring. These tumors are highly vascularized with both blood and lymphatic vessels. Angiogenesis (the formation of blood vessels) and lymphangiogenesis (the formation of lymphatic vessels) are important for the growth and spread of cancerous tumors, but little is known about angiogenesis and lymphangiogenesis in TSC. In experimental models, drugs that inhibit angiogenesis and lymphangiogenesis have decreased the size and spread of cancers. Dr. Thomas Darling hypothesizes that similar treatment could inhibit skin tumors in TSC patients. Dr. Darling's laboratory has found that TSC skin tumors produce higher-than-normal levels of proteins that stimulate angiogenesis and lymphangiogenesis. Rapamycin and tranilast have been used for the treatment of TSC-related tumors with varying success. The mechanisms by which rapamycin and tranilast exert their effects on the processes of angiogenesis and lymphangiogenesis are not completely understood. Dr. Darling plans to test the effects of rapamycin on the production of proteins involved in angiogenesis and lymphangiogenesis in TSC skin tumors. He also plans to test the effectiveness of tranilast in blocking angiogenesis and lymphangiogenesis in TSC skin tumors. To test the effects of rapamycin and tranilast on TSC skin tumors, Dr. Darling will use early-passage primary TSC2-null cells grown from human TSC skin tumors in his novel xenograft mouse model. This model system will allow for quantification of the tumor microenvironment in response to experimental manipulations. Dr. Darling will use more than one human cell type in these grafts (TSC tumor cells, normal human keratinocytes, and melanocytes), making these more representative of the human tumor. If successful, Dr. Darling's work would have three potential clinical applications: (1) a better understanding of how rapamycin and tranilast inhibit tumor growth in TSC, (2) a determination as to whether rapamycin and tranilast have a synergistic effect when combined, and (3) identification of proteins that would be useful in blood tests to determine if tumors are responding to treatment.



Retaining Young Scientists in TSC Research

Career Transition Award

Protein Synthesis-Dependent Synaptic Changes in Tuberous Sclerosis Complex

Akira Yoshii, M.D., Ph.D.
Massachusetts Institute of Technology
FY08 Career Transition Award Recipient

Patients with TSC have nonmalignant brain tumors called cortical hamartomas. Cortical hamartomas often become the focus of seizures in TSC patients, leaving some aspects of TSC's neurological features unexplained. Dr. Akira Yoshii is studying whether it is neurons themselves that are malfunctioning in TSC. Neurons communicate with each other at junctions called synapses. At a synapse, one neuron releases neurotransmitters and another neuron receives the signal via its receptors. There are excitatory and inhibitory synapses, which normally exist in equilibrium; however, in seizures excitation overwhelms neural circuitry. This type of imbalance is also thought to cause autistic behavior. Dr. Yoshii plans to test the hypothesis that the balance between excitation and inhibition is skewed in TSC and that this synaptic dysregulation is caused by altered protein synthesis. To test this hypothesis, Dr. Yoshii will use biochemical assays to determine the levels of both excitatory and inhibitory synapse-associated proteins in brains of TSC mutant mice compared to wild-type (normal) mice. He will look for evidence of upregulation of excitatory synaptic proteins and/or downregulation of inhibitory synaptic proteins. Rapamycin, an mTOR inhibitor, has been reported to be beneficial for seizure control and the overall health of TSC mutant mice. Dr. Yoshii plans to examine whether rapamycin will affect surface expression of excitatory and inhibitory receptors. Results of these experiments will potentially advance understanding of the neurobiological basis of TSC and facilitate the identification of a therapeutic target for neurological symptoms of this challenging disorder.

Impacting Patients' Lives

Natural History Studies: Developing a Comprehensive Clinical Database

Steven Sparagana, M.D.
Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center at Dallas
FY04 Natural History Development Award Recipient

Dr. Steven Sparagana of Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center at Dallas began development of a TSC Natural History Database using funds from a FY04 Natural History Development Award in collaboration with the TS Alliance and a consortium of health care professionals from TSC clinics. The database was piloted at two TSC clinics (Minnesota Epilepsy Group, PA® and Texas Scottish Rite Hospital for Children) in 2006. There are now 15 TSC clinics, including the first foreign clinic site (UZ Brussels Hospital, Brussels, Belgium), and the TS Alliance is currently leading this project. As of July 2009, more than 800 people have been enrolled in the project, nearly 70 percent of whom are children less than 18 years old. This comprehensive clinical database of TSC documents the natural history and variability of TSC over the lifespan of individuals with the disease. Information collected for the database from each study participant includes demographics, enrollment in the database, initial TSC diagnosis, genotype, participation in investigational studies, mortality, family history, prenatal history, vital signs, TSC-related diagnoses, diagnostic tests, and treatments. Understanding the clinical aspects of TSC could lead to more accurate disease prognosis, the development of new targeted therapies, and the prediction of an individual's response to treatments.

The Program Today

The Vision for FY09

In FY09, $6M was appropriated to the TSCRP for research by Congress. The TSCRP encourages innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC. Four award mechanisms encompassing this overall mission were offered in FY09 to fill important gaps in TSC research and accelerate discoveries.

FOCUS	AWARD MECHANISM
Clinical Research 	*Clinical and Translational Research Award*: Supports either clinical/translational research studies or clinical trials. Multidisciplinary collaborations are encouraged to bring in new perspectives from other disciplines or bring new investigators into the field.
Innovative Research 	*Exploration-Hypothesis Development Award*: Supports the initial exploration of innovative, untested, high-risk, high-gain, and potentially groundbreaking concepts in TSC research.
	Idea Development Award: Supports high-impact, innovative research that will drive the TSC field forward.
Career Development 	*Career Transition Award*: Supports TSC researchers during the transition from postdoctoral training to an independent position.

For more information, contact
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